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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/662,790
Filing Date: September 15, 2000
Appellant(s): CHANDLER ET AL.

Ann Marie Mewherter
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3 March 2006 appealing from the Office action mailed 29 June 2005.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The outstanding rejection under 35 USC 112, 2nd paragraph is withdrawn in view of Appellant's arguments.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

Kettman et al (Cytometry (1998) Vol. 33, pages 234-243)

Ekins et al. (Journal of Pharmaceutical and Biomedical Analysis (1989) Vol. 7, pages 155-168).

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.

2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7, 40 and 41 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Kettman et al (Cytometry (1998) Vol. 33, pages 234-243) in view of Ekins et al. (Journal of Pharmaceutical and Biomedical Analysis (1989) Vol. 7, pages 155-168).

Kettman et al. teach a method and system for analysis of multiple analytes in a single sample, as recited in claims 1-7. (see abstract, page 234). "The vehicle for each separate measurement consists of a set of microspheres identifiable by characteristic fluorophores embedded in the particles. The use of robust bench-top flow cytometers for the analysis of the multiple sets of microspheres is facilitated by hardware and software, which acquire the data from cytometer, classify the microspheres according to sets, and collate measurement information for each set of microspheres in real time. This measurement system can analyze up to 64 analytes in a single sample". Kettman et al. teach a method for the analysis of multiple analytes in a single sample in which the vehicle for each separate measurement consists of a set of microspheres identifiable by their characteristic fluorophores embedded in the particles

(abstract, column 1). Kettman et al. describe the design and construction of the FlowMetrix3 microspheres on page 325, column 2. Specifically, the molecules attached to the microsphere surface are called the "target" molecules and consist of two fluorescent dyes (orange and red). The labeled molecules that bind the microsphere are called the "reporter" (green). Furthermore, Ketmann et al. also describe that these panels are useful for analysis of antibodies, antigens, and other soluble molecules, including nucleic acids, drugs, and enzymes (see introduction).

Kettman et al. do not teach 75, 100, 200, 300 or more subsets of microspheres or 75 analytes in an analysis. However, Ekins teaches a multi-analyte immunoassay in which tens or hundreds of substances can be measured simultaneously (abstract), therefore suggesting increasing the analyte and microsphere values in order to increase the capability of medical diagnosis and drug design, for example. It would have been prima facie obvious to one of ordinary skill in the art at the time if invention to have incorporated more than 75 analytes/microspheres into the invention of Kettman et al., as suggested by Ekins. One would be motivated to do so by the teachings of Ekins, which state that "fluorescent labels are particularly useful in this context because they readily permit arrays of different antibody "microspots" distributed over a surface, each directed against a different analyte, to be individually examined, thus enabling multiple assays to be simultaneously carried out on the same small sample. The same principals are clearly applicable using other forms of label (page 166, lines 16-21)". One of ordinary skill in the art would have reasonably expected success in using hundreds of microspheres because Ekins teaches, "it is both conceivable and within the range of present technology that immunoprobes will be developed capable of measuring every hormone (or iso-hormone component), together with other endocrinologically related substance within a single

small sample of blood, providing data which, when analyzed with the aid of computer based "expert" pattern recognition systems, will reveal endocrine deficiencies only dimly perceived using current "single analyte" diagnostic procedures (page 167, lines 12-19)".

(10) Response to Argument

Rejections under 35 USC 103(a)-Kettman in view of Ekins

A.

1. Appellants argue that the prior art does not teach, suggest, or provide motivation for a Multi-Analyte Profile (MAP) Test Panel that includes 75 or more subsets of microspheres. Appellant argues that there is no suggestion or motivation, whether in the references themselves or in the knowledge generally available to one of ordinary skill in the art to combine Kettman and Ekins as suggested in the Final Office Action.

This is not persuasive as the Examiner clearly set forth a motivation for the combination of references in the Office Action dated 6 July 2004, which is re-iterated above. Furthermore, the Examiner disagrees with Appellant's statement that Kettman "discloses that the number of microsphere sets that can be used in a multiplexed array is limited by the uniformity of the microspheres and that the median MFI of the population should be placed as close to the center of the classification criteria as possible". Further, Appellant argues that "microspheres from one set do not fall into the classification criteria for a neighboring set of microspheres and that this feature is related to the uniformity of the fluorescence among the members of each microsphere set". Appellant concludes that "the number of microsphere sets that can be used in a multiplexed array is limited by the fluorescence uniformity among the microsphere members of each set".

This is not persuasive because Kettman teaches that "the more uniform the population, the more sets can be blended (page 239, column 1 to column 2). This is not the same as what Appellant has concluded. There are no limitations set by Kettman with regard to how many sets can be blended, even though in the example, 64 sets were used. The limitation comes with regard to uniformity of those sets. However, the instant claims do not recite any limitation with regard to the uniformity of microspheres. Furthermore, the rejection as set forth above relies upon Ekins to teach the limitation that more than 75 sets may be examined in a multi-analyte test profile.

Appellant argues that "Kettman teaches that variations in the microspheres themselves and the dye content within the microspheres affect the fluorescence used to determine the set to which the microsphere belongs and consequently Kettman teaches that the number of microsphere sets that can be included in an assay is limited at least in part by the variations in the microspheres themselves and the dye content within the microspheres. The limitations in the number of microsphere sets that can be used in an assay disclosed by Kettman is perhaps why Kettman states that 'This measurement system can analyze up to 64 analytes in a single sample' using 64 multiplexed microsphere sets".

This is not persuasive. The instant claims are drawn to a multi-analyte profile test panel comprising 75 or more subsets of microspheres, wherein one subset is distinguishable from another subset by their characteristic fluorescence signatures and wherein the microspheres of one subset are coupled to at least one reagent designed to interact selectively with a predetermined analyte. As stated above, Kettman teaches a multiple-analyte profile test panel for multiple analytes in a single sample in which the vehicle for each separate measurement

consists of a set of microspheres identifiable by their characteristic fluorophores embedded in the particles. There are 64 microsphere sets in the teaching of Kettman. The microsphere sets are not limited by their number. Rather, they are limited by the dye content, as stated by Appellant. Kettman teaches that "reliable classification of the sets depends on each set producing its characteristic level of fluorescence and the instrument amplifying those signals (page 241, column 2)". Kettman does not limit the number of microsphere sets that can be used. The number of analytes measured was up to 64, however, Kettman does not teach away from using more than 64 microsphere sets. The limitations to which Appellant is pointing with regard to dye content and how fluorescence is imparted are not limitations found in the instant claims. Furthermore, it is Ekins who is relied upon to teach that more that 75 sets may be used in analyte analysis.

Appellant further states, in regard to Ekins, that a "multi-analyte immunoassay that utilizes antibody molecules attached to a solid support is disclosed". Appellant contends that "unlike the assay of Kettman in which fluorescent markers are dissolved within the solid substrate (e.g., microspheres), the markers used by Ekins are not dissolved or otherwise integrated into a solid substrate". Therefore, Appellant concludes, "unlike the assays of Kettman, which as taught by Kettman are limited at least in part by the variations in the microspheres themselves and the dye content within the microspheres, Ekins appears to teach that using fluorescently labeled antibodies located externally to a solid substrate in an assay does not limit the assay to measuring up to 64 analytes in one sample".

This is not persuasive. It is again pointed out that there are no limitations within the instant claims as to how fluorescence is imparted and therefore, the argument is not relevant to

the instant claim set. Further, Ekins is relied upon to teach that, in fact, in multi-analyte analysis, sets of more than 75 may be analyzed, despite the assay type. In fact, Ekins states that "immunoassay methodologies are very closely comparable, both in principal and practice, to other forms of 'binding assay' in which classes of specific binding protein (serum binding proteins, hormone receptors, enzymes, etc.) are substituted for antibodies as the key analytical agent in the system. On close examination of the range of methodologies currently available for the measurement of biomolecules, there are no clear dividing lines between them (page 156, paragraph 1)".

Therefore, claims 1-7, 40 and 41 are unpatentable over Kettman in view of Ekins.

2. Appellant argues that "Ekins does not teach any microspheres at all. For instance, Ekins teaches different antibodies distributed over a single surface, each of which is specific to a different analyte being examined. Ekins teaches more that 64 different antibodies, each coupled to the same surface, but Ekins clearly does not teach 'more that 64 sets' in analyte analysis".

This is not persuasive. Ekins is not relied upon to teach microspheres, as is stated above. Microspheres are taught by Kettman; Ekins teaches that it is possible to analyze simultaneous measurement of tens or even hundreds of substances in the same small sample (page 155, paragraph 1). Further, Kettman acknowledges that the use of such [microsphere] assays affords advantages in the multiplex analysis of antibodies, antigens, and other soluble molecules, including nucleic acids, drugs, and enzymes. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have assessed more that 64 sets of

microspheres for multiplex analysis, whether for antibody detection or some other soluble molecule, as motivated by the teaching above.

3. Appellant argues that the prior art appears to teach away from the combination of Kettman and Ekins. Appellant states that "even if the fluorescent markers of Ekins could be coupled to the surface of the microspheres of Kettman, the prior art appears to teach away from such a modification of the microspheres of Kettman".

This is not persuasive. As stated above and in the office action of 6 July 2004, Ekins is not relied upon to teach the attachment of markers to the microspheres. Ekins is relied upon to teach that more than 75 sets may be examined, whether it is 75 sets of antibodies or some other vehicle.

4. Appellant argues that the prior art references must be considered in their entirety. Further Appellant states that "Ekins does not teach sets that can be used in analyte analysis". In addition, Appellant argues that "regardless of how fluorescence is imparted to the presently claimed subsets of microspheres, the manner in which fluorescence is imparted to the assays in the prior art must be considered to determine if a reasonable expectation of success is taught or suggested by the prior art for more that 64 sets".

This is not persuasive. Ekins clearly teaches that the development of the multi-analyte immunoassay system allows the measurement of tens or hundreds of substances. In the immunoassay, a substance (analyte) to be measured is reacted with a specific antibody directed against it. The analyte concentration is deduced from the products of the binding reaction. Ekins states that "there are no clear dividing lines between the range of methodologies available for the

measurement of biomolecules (page 156, paragraph)". It is well known in the art that antibodies may be attached to solid supports, such as microspheres. Ekins states that it is ideal, for instance, in the case of an ambient analyte assay to have the antibody attached to a solid support (page 164, paragraph 1).

Further, there is no requirement in the instant claims for the manner in which the fluorescence is imparted to the assays. Therefore, this argument is not persuasive, as it does not relate to the claimed subject matter. Further, Kettman teaches the embodiment of fluorescent attachment to microspheres, at page 235, column 2 to 236, column 1. The Examiner maintains that one of skill in the art at the time of the invention would have reasonably expected success in combining Ekins and Kettman, for the reasons set forth above.

5. Appellant argues that the prior art references, considered in their entirety, do not provide a reasonable expectation of success for combining the prior art as suggested in the Final Office Action. Appellant further argues that the manner in which fluorescence is imparted is critical to the expectation of success.

However, this is not persuasive, as Kettman teaches the manner in which one would impart fluorescence to a set of microspheres. Ekins teaches that the development of the multi-analyte immunoassay system allows the measurement of tens or hundreds of substances, as stated above. Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of the invention to have assessed more that 64 sets of microspheres for multiplex analysis. Further, the claims are not limited to the method by which fluorescence is imparted. One of skill in the art would have had a reasonable expectation of success in combining the

methods of Kettman with the detection of multiple analytes because both teach detection of fluorescently labeled analytes and because the prior art of Kettman specifically teaches how to impart fluorescence to the microspheres using the same method disclosed by Applicant.

6. Appellant argues that since the teachings in the prior art conflict, the power of each reference to suggest solutions to one of ordinary skill in the art must be considered. Further, Appellant states that the teachings of Kettman and Ekins conflict as to appropriate fluorescent labels that can be used to create probes for measurements of multiple substances in a single sample.

This is not persuasive, as has been stated above. The claims do not recite specific limitations for labels that can be used to create probes.

7. Appellant argues that the cited art does not suggest the desirability of the combination of the teachings of Kettman and Ekins. Appellant further argues that for the reasons above, Kettman and Ekins cannot be combined.

This is not persuasive, as has been addressed above.

8. Appellant argues that since there is no objective reason to combine the teachings of the references, even if the references teach all of the aspects of the claimed invention were individually known in the art, the references are not sufficient to establish a *prima facie* case of obviousness.

This is not persuasive for the reasons set forth above. The Examiner has established a prima facie case of obviousness based upon the teachings of Kettman in combination of Ekins fir the reasons and motivations set forth above.

9. Appellant states that the Examiner has failed to adequately support and/or establish a *prima facie* case of obviousness.

This is not persuasive, as stated above. The Examiner has clearly set forth a prima facie case of obviousness based upon the teachings of Kettman in combination with Ekins. The Examiner has clearly set forth a motivation to combine and a clear expectation of success. See the rejection above under 35 USC 103(a).

B.

1. Appellant argues that the cited art does not teach or suggest microspheres of one subset that are distinguishable from those of another subset by their characteristic fluorescence signatures derived from at least three fluorescent dyes incorporated into the microspheres.

This is not persuasive. Kettman clearly teaches a multiplexed system using three parameters in which orange fluorescence and red fluorescence classify FlowMetrix microspheres. In addition, green fluorescence was measured (page 234, column 1).

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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